

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,037,721 B1
APPLICATION NO. : 09/694393
DATED : May 2, 2006
INVENTOR(S) : John J. Wille, Jr.

Page 1 of 12

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In section (56), please add the following U.S. Patent Documents initialed by the Examiner on September 20, 2001 and inadvertently not cited in the patent as follows:

4,009,282	02/22/77	Voorhees	514/573
4,016,036	04/05/77	Green, et al.	195/1.8
4,088,756	05/09/78	Voorhees	514/047
4,201,788	05/06/80	Voorhees, et al.	514/081
4,209,315	06/10/80	Voorhees, et al.	514/047
4,304,866	12/08/81	Green, et al.	435/240
4,485,096	11/27/84	Bell	424/95
4,673,649	06/16/87	Boyce, et al.	435/240
4,940,666	07/10/90	Boyce, et al.	435/240.2
5,232,848	08/03/93	Wolfe, et al.	435/240.31
5,292,655	03/08/94	Wille, Jr.	435/240.2
5,326,699	07/05/94	Torishima, et al.	435/240.2
5,328,844	07/12/94	Moore	435/240.31
5,604,346	8/86	Bell, et al.	435/1
5,683,307	11/11/97	Wille, Jr.	435/405
5,834,312	11/10/98	Wille, Jr.	435/405
5,871,909	02/16/99	ANG.strom, et al.	435/006
6,063,606	05/2000	Martin, et al.	435/189

In section (56), please add -- OTHER PUBLICATIONS

“Production of Epidermal Sheets in a Serum Free Culture System: A further appraisal of the role of extracellular calcium,” *Journal of Dermatological Science*, 3, Boisseau, et al., Elsevier Science Publishers V.V. (1992) 111-120.

“Reagents, Suppliers and Media Formulations,” *Catalogue of Cell Lines & Hybridomas*, American Type Culture Collection, 6th Ed. 1988, pp. 342-343.

“Production and auto-induction of transforming growth factor- α in human keratinocytes,” Coffey, Jr., et al., *Nature*, Vol. 328, 27 August 1987, pp. 817-820.

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In section (56), please add -- OTHER PUBLICATIONS (cont'd)

"Growth and Differentiation of Human Keratinocytes Without a Feeder Layer or Conditioned Medium," Peehl, et al., *In Vitro*, 1616: 516-525; 1980.

"Improved Medium and Culture Conditions for Clonal Growth with Minimal Serum Protein and for Enhanced Serum-Free Survival of Swiss 3T3 Cells," Shipley, et al., *In Vitro*, Vol. 17, No. 8, August 1981: 1981 Tissue Culture Association, Inc., pp. 656-670.

"Buffer Combinations for Mammalian Cell Culture," *Science*, Vol. 174, pp. 500-503.

"Cultured Cells for Treatment of Disease," Green, *Scientific American*, Nov. 1991, pp. 96-102.

"Culture of Human Keratinocytes in Defined Serum-Free Medium," Judd, et al., *Focus*, 19 No. 1 (1997), pp. 2-5.

"Cultured Composite Skin Grafts: Biological Skin Equivalents Permitting Massive Expansion," Nanchahal, et al., *The Lancet*, July 22, 1989, pp. 191-193.

"Growth of Cells in Defined Environments: The Role of Endogenous Production of Insulin-like Growth Factors," Nissley, et al., *Growth & Differentiation of Cells in a Defined Environment* (1985) pp. 337-344.

"Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium," Pellegrini, et al., *The Lancet*, Vol. 349, April 5, 1997, pp. 990-993.

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In section (56), please add -- OTHER PUBLICATIONS (cont'd)

"Calcium-Regulated Differentiation of Normal Human Epidermal

Keratinocytes in Chemically Defined Clonal Culture and Serum-Free Serial Culture,"

Boyce, et al., *The Journal of Investigative Dermatology*, Boyce, et al., Vol. 81, No. 1

Supplement (1983), pp. 33s-40s.

"Cultivating a Cure for Blindness," Hodson, *Nature*, Vol. 387, May 1997, p. 449.

"Clonal Growth of Normal Human Epidermal Keratinocytes in a Defined Medium," Tsao, et al., *Journal of Cellular Physiology* 110:219-229 (1982).

"Ability of Normal Human Keratinocytes that Grow in a Culture in Serum-Free Medium to be Derived from Suprabasal Cells," Wilke, et al., *Journal of the National Cancer Institute*, Vol. 80, No. 16, Oct. 1988, pp. 1299-1304.

"Biologic Mechanisms for the Regulation of Normal Human Keratinocyte Proliferation and Differentiation," Wilke, et al., *American Journal of Pathology*, Vol. 131, April 1988, pp. 171-181.

"Effects of Growth Factors, Hormones, Bacterial Lipopolysaccharides, and Lipotechoic Acids on the Clonal Growth of Normal Ureteral Epithelial Cells in Serum-Free Culture," Wille, et al., *Journal of Cellular Physiology*, 150:52-58 (1992).

"Integrated Control of Growth and Differentiation of Normal Human Prokeratinocytes Cultured in Serum-Free Medium: Clonal Analyses, Growth Kinetics, and Cell Cycle Studies," Wille, Jr., et al., *Journal of Cellular Physiology*, 121:31-44 (1984).

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In section (56), please add -- OTHER PUBLICATIONS (cont'd)

"Propagation of Differentiating Normal Human Tracheobronchial Epithelial Cells in Serum-Free Medium," Chopra, et al., *Journal of Cellular Physiology* 130: 173-181 (1987).

"Reversible Inhibition of Normal Human Prokeratinocyte Proliferation of Type β Transforming Growth Factor-Growth Inhibitor in Serum-free Medium," Shipley, et al., *Cancer Research* 46, 2068-2071, April, 1986.

"Serum-Free Cultures of Normal Human Gingival Keratinocytes (HGK)," Wille, et al., *Journal of Dental Research*, 68, 1019, #1216.

"Two Functionally Distinct Classes of Growth Arrest States in Human Prokeratinocytes that Regulate Clonogenic Potential," Pittelkow, et al., *Journal of Investigative Dermatology*, Vol. 4, April, 1986, pp. 410-417.

Moses, et al. "Growth & Differentiation of Cells in Defined Environment (1985) pp. 373-378.

Booyens, et al, "Prostaglandins Leukot. Md., " Jul. 1984, 15 (1) pp. 15-33 (Biosis Abstract #84298492).

The Merck Index, 10th edition, 1983, p. 1172.

Boyce & Ham, *J. Invest. Dermatol.* 81:33-40, 1983 Ca-Reg. differentiation of normal human epid. Keratin In chemical & serum defined Med.

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In section (56), please add -- OTHER PUBLICATIONS (cont'd)

"All-Trans Retinoic Acid Stimulates Growth of Adult Human Keratinocytes Cultured in Growth Factor-Deficient Medium, Inhibits Production of Thrombosondin in Fibronectin, and Reduces Adhesion," Varani, et al. *The Society for Investigative Dermatology, Inc.*, 0022-202X/89/S03.50 (1989).

Rikimaru, et al. "Growth of malignant and nonmalignant human squamous cells in a protein-free defined medium, *In Vitro Cell Dev. Biol.*, 26(9):849-56, Sept. 1990 (Medline Abstract).

Diaz, et al. "Regulation of vascular endothelial growth factor expression in human keratinocytes by retinoids, *J. Biol. Chem.* 275(1):642-50, Jan. 7, 2000 (Medline Abstract).

Stoll, et al. "Retinoid regulation of heparin-binding EGF-like growth factor gene expression in human keratinocytes and skin," *Exp. Dermatol.* 7(6):3917, Dec. 1998 (Medline Abstract).

Marcello, et al., "Retinoic acid stimulates essential fatty acid-supplemented human keratinocytes in culture," *J. Invest. Dermatol.*, 108(5):758-62 May 1997 (Medline Abstract).

Jetten "Multi-stage program of differentiation in human epidermal keratinocytes: regulation by retinoids," *J. Invest. Dermatol.*, 85(5):44S-46S Nov. 1990 (Medline Abstract).

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In section (56), please add -- OTHER PUBLICATIONS (cont'd)

Jee, et al., "Growth and characterization of normal human keratinocytes in F12 serum-free medium," *J. Formos Med. Assoc.* 89(7):559-64 July 1990 (Medline Abstract).

Varani, "Preservation of human skin structure and function in organ culture," *Histol. Histopathol.* 13(3):775-83 July 1998 (Medline Abstract).

Siegenthaler, et al. "Retinol and retinal metabolism. Relationship to the state of differentiation of cultured human keratinocytes," *Biochem J.* 268(2):371-8 June 1, 1990 (Medline Abstract).

Lachgar, et al. "Inhibitory effects of retinoids on vascular endothelial growth factor production by cultured human skin keratinocytes," *Dermatology* 199 Suppl. 1:25-7 1999 (Medline Abstract).

Imanishi, et al. "Growth factors: importance in wound healing and maintenance of transparency of the cornea," *Prog. Retin Eye Res.* 19(1):113-29 Jan. 2000 (Medline Abstract).

Johnson, et al. "Persistence of fetal bovine serum proteins in human keratinocytes," *J. Burn Care Rehabil.*, 11(6) 504-9 Nov.-Dec. 1990 (Medline Abstract).

Schwartz "In vitro growth changes of oral human keratinocytes after treatment with carotenoids, retinoid, and/or DMBA," *Nutr. Cancer*, 33(1):58-68 1999 (Medline Abstract).

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In section (56), please add -- OTHER PUBLICATIONS (cont'd)

Sass, et al. "Metabolism of topical retinaldehyde and retinol by mouse skin in vivo: predominant formation of retinyl esters and identification of 14-hydroxy-4, 4-retro-retinol," *Exp. Dermatol.* 5(5):267-71, Oct. 1996 (Medline Abstract).

Marikar, et al. "Retinoic acid receptors regulate expression of retinoic acid 4-hydroxylase that specifically inactivates all-trans retinoic acid in human keratinocyte HaCaT cells," *J. Invest. Dermatol.*, 111(3):434-9 Sept. 1998 (Medline Abstract).

Griffiths, et al. "Short-term retinoic acid treatment increases in vivo, but decreases in vitro, epidermal transglutaminase-K enzyme activity and immunoreactivity," *J. Invest. Dermatol.* 99(3):283-8 Sept. 1992 (Medline Abstract).

Duell, et al. "Human skin levels of retinoic acid and cytochrome P-450-derived 4-hydroxyretinoic acid after topical application of retinoic acid in vivo compared to concentrations required to stimulate retinoic acid receptor-mediated transcription in vitro," *J. Clin. Invest.* 90(4): 1269-74 Oct. 1992 (Medline Abstract).

Duell, et al. "Unoccluded retinol penetrates human skin in vivo more effectively than unoccluded retinyl palmitate or retinoic acid," *J. Invest. Dermatol.* 109(3):301-5 Sept. 1997 (Medline Abstract).

Kang, et al. "Liarozole inhibits human epidermal retinoic acid 4-hydroxylase activity and differentially augments human skin responses to retinoic acid and retinol in vivo," *J. Invest. Dermatol.* 107(2):183-7 Aug. 1996 (Medline Abstract).

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In section (56), please add -- OTHER PUBLICATIONS (cont'd)

Kurlandsky, et al; "Auto-regulation of retinoic acid biosynthesis through regulation of retinol esterification in human keratinocytes," *J. Biol. Chem.* 271(26):15346-52 June 28, 1996 (Medline Abstract).

Varani, et al. "A direct comparison of pharmacologic effects of retinoids on skin cells in vitro and in vivo," *Skin Pharmacol.* 4(4):254-61 1991 (Medline Abstract).

Varani, et al. "Retinoic acid stimulation of human dermal fibroblast proliferation is dependent on suboptimal extracellular Ca²⁺ concentration," *Am. J. Pathol.* 136(6):1275-81 June 1990 (Medline Abstract).

Varani, et al. "All-trans retinoic acid stimulates growth and extracellular matrix production in growth-inhibited cultured human skin fibroblasts," *J. Invest. Dermatol.* 94(5):717-23 May 1990 (Medline Abstract).

Wang, et al. "Ultraviolet irradiation of human skin causes functional vitamin A deficiency, preventable by all-trans retinoic acid pre-treatment," *Nat. Med.* 5(4):418-22 April 1999 (Medline Abstract).

Xiao, et al. "Identification of heparin-binding EGF-like growth factor as a target in intercellular regulation of epidermal basal cell growth by suprabasal retinoic acid receptors," *EMBO J.* 18(6):1539-48 March 15, 1999 (Medline Abstract).

Griffiths, et al. "Mechanisms of action of retinoic acid in skin repair," *Br. J. Dermatol.* 127 Suppl 4:21-4 Sept. 1992 (Medline Abstract).

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In section (56), please add -- OTHER PUBLICATIONS (cont'd)

Varani, et al. "Induction of proliferation of growth-inhibited keratinocytes and fibroblasts in monolayer culture by sodium lauryl sulfate: comparison with all-trans retinoic acid," *J. Invest. Dermatol.* 97(5):917-21 Nov. 1991 (Medline Abstract).

Fligiel, et al. "Modulation of growth in normal and malignant melanocytic cells by all-trans retinoic acid," *J. Cutan Pathol.* 19(1):27-33 Feb. 1992 (Medline Abstract).

Varani, et al. "Inhibition of epithelial cell adhesion by retinoic acid.

Relationship to reduced extracellular matrix production and alterations in Ca²⁺ levels," *Am. J. Pathol.* 138(4):887-95 April 1991 (Medline Abstract).

Varani, et al. "Modulation of Ca²⁺ levels in keratinocytes by all-trans retinoic acid," *Pathobiology* 60(2):93-9 1992 (Medline Abstract).

Varani, et al. "Molecular mechanisms of intrinsic skin aging and retinoid-induced repair and reversal," *J. Invest. Dermatol. Symp. Proc.* 3(1):57-60 Aug. 1998 (Medline Abstract).

Tavakkol, et al. "Expression of growth hormone receptor, insulin-like growth factor 1 (IGF-1) and IGF-1 receptor mRNA and proteins in human skin," *J. Invest. Dermatol.* 99(3):343-9 Sept. 1992 (Medline Abstract).

Fisher, et al. "Molecular mechanisms of retinoid actions in skin," *FASEB J.* 10(9):1002-13 July 1996 (Medline Abstract).

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In section (56), please add -- OTHER PUBLICATIONS (cont'd)

Sasaki, et al. "Enhancement by 1 alpha,25-dihydroxyvitamin D₃ of chemically induced transformation of BALB 3T3 cells without induction of ornithine decarboxylase or activation of protein kinase C1," *Cancer Res.* 46(2):604-10 Feb. 1986 (Medline Abstract).

Kamata, et al. "Growth of normal oral keratinocytes and squamous cell carcinoma cells in a novel protein-free defined medium," *In Vitro Cell Dev. Biol Anim.* 35(10):63-41 Nov.-Dec. 1999 (Medline Abstract).

Goi, et al "DNA damage-associated dysregulation of the cell cycle and apoptosis control in cells with germ-line p53 mutation," *Cancer Res.* 57(10):1895-902 May 15, 1997 (Medline Abstract).

Kurata, et al. "Effect of eicosapentaenoic acid and arachidonic acid on mouse peritoneal exudate cells and its characteristics," *Yakugaku Zassi* 106(11):1040-4 Nov. 1986 (Japanese language—copy not available) (Medline report).

Kamata, et al. "Growth-inhibitory effects of epidermal growth factor and overexpression of its receptors on human squamous cell carcinomas in culture," *Cancer Res.* 46(4 Pt 1):1648-53 April 1986 (Medline Abstract). --

In section 73, please delete "Hy-Gene Biomedical, Inc., Charlotte, NC (US)" and insert -- Hy-Gene Biomedical Corporation, Ventura, CA (US) --.

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In section 74, please delete "Standley & Gilcrest LLP" and insert -- Standley Law Group LLP --.

In column 7, line 20, please delete "0.01" and insert-- 0.1 --.

In column 10, line 52, please delete "speed-centrifugation," and insert-- speed centrifugation --.

In column 12, in Table 1, please delete "Pyridoxal.HCl" and insert -- Pyridoxal.HCl--.

In column 12, in Table 1, please delete "Thiamine.HCl" and insert -- Thiamine.HCl --.

In column 12, in Table 1, please delete "Calcium chloride.2H₂O" and insert -- Calcium chloride·2H₂O --.

In column 12, in Table 1, please delete "Magnesium chloride.6H₂O" and insert -- Magnesium chloride·6H₂O --.

In column 12, in Table 1, please delete "Ferrous sulfate.7H₂O" and insert -- Ferrous sulfate·7H₂O --.

In column 12, in Table 1, please delete "Manganese Sulfate.5H₂O" and insert -- Manganese Sulfate·5H₂O --.

In column 12, in Table 1, please delete "Sodium Silicate.9H₂O" and insert -- Sodium Silicate·9H₂O --.

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 12, in Table 1, please delete “Ammonium Molybdate.4H₂O” and insert -- Ammonium Molybdate·4H₂O --.

In column 12, in Table 1, please delete “Nickel Chloride.6H₂O” and insert -- Nickel Chloride·6H₂O --.

In column 12, in Table 1, please delete “Zinc Chloride.7H₂O” and insert -- Zinc Chloride·7H₂O --.

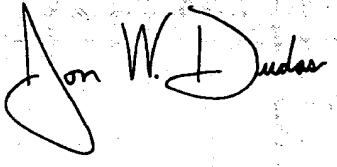
In column 12, in Table 1, please delete “Sodium Acetate.3H₂O” and insert -- Sodium Acetate·3H₂O --.

In column 14, in line 19, please delete “(J”.

In column 16, in line 21, please delete “HPO₄.sub.4.7H₂O” and insert-- HPO₄.sub.4.7H₂O --.

Signed and Sealed this

Fourteenth Day of November, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office